REMARKS

Claims 1, 4, 8-10, 12, 17, 28-30, 43-46, 49, 50, 53-60, and 63-68 were pending as of the issuance of the Office Action dated July 10, 2009. Claims 1, 28, 43, 44, 49, 56, 59, and 66 have been amended. New claim 69 has been added. Accordingly, claims 1, 4, 8-10, 12, 17, 28-30, 43-46, 49, 50, 53-60, and 63-69 are currently pending in this application.

Support for the foregoing amendments to the claims, as well as for the new claims, can be found throughout the specification and claims as originally filed. For example, support for the amendments to claims 1, 43, 44, 49 and 59, as well as for new claim 69, can be found at least at Figure 2 and 23; page 20, line 25 through page 21, line 4; Table 1; and Example 5. Applicants submit that no new matter has been added by the claim amendments presented herein.

Withdrawal of Certain Rejections

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection of claim 49 under 35 U.S.C. 112, 2nd paragraph, as well as the withdrawal of the rejection of claims 1, 4, 6-10, 12, 17, 28-30, 41-46, and 49-68 under 35 U.S.C. 112, 1st paragraph.

Examiner Interview

Applicants extend their thanks to Examiner Gussow for her courtesy in conducting a personal interview with Applicants' representative, Debra Milasincic, on September 30, 2009 to discuss the outstanding rejections under 35 U.S.C. §103(a). Applicants' response to these rejections is provided below.

Claim Objections

The Examiner has noted that line 2 of claim 1 implements improper Markush group language. Applicants have amended claim 1 to delete "/or" thereby addressing the Examiner's concerns. Applicants respectfully request that this objection be withdrawn. Similar amendments have been voluntarily made to claims 28, 44, 56, and 66.

Claim Rejections Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 4, 8-10, 12, 17, 43-46, 49, 50, 53-60, and 63-68 under 35 U.S.C. § 103(a) as being unpatentable over Houimel *et al.* 2001 (International Journal of Cancer, vol. 92, pages 748-55) in view of Wickham *et al.* 2002 (U.S. Publication No. 2003/0099619), Koh 2006 (U.S. Patent No. 7,081,443), Rusch *et al.* 1996 (Cytokine and Growth Factors Review, vol. 7, pages 133-41), and Todaro *et al.* 1986 (EP 0190018). The Examiner has argued that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a peptabody comprising the cartilage oligomer matrix polypeptide (COMP), hinge and peptabody structure of Houimel *et al.* with the peptide sequence of Wickham *et al.*, the fluorescent tag of Koh, and the ligand sequence of Todaro *et al.* for diagnosing and treating breast cancer. Applicants respectfully traverse.

The Examiner has stated on page 5 (lines 7-16) that:

> "Houimel *et al.* teach a recombinant peptabody that binds to ErbB2 comprising a human cartilage oligomeric matrix protein (COMP) identical to residues 16 to 64 of SEQ ID No.2, a hinge region derived from human IgA1 identical to residues 65 to 83 of SEQ ID No. 2 and a polyhistidine tag sequence (figure 2). Houimel *et al.* teach targeting of breast cancer cells with the peptabody (figure 5). Houimel *et al.* do not teach the enhancer sequences of SEQ ID Nos 5, 6 and 9, or the ligand sequences of SEQ ID No's ID 10-29. Houimel *et al.* do not teach the peptabody fused to a fluorescent tag or in a pharmaceutical composition. (emphasis added)"

Applicants respectfully disagree with the Examiner's position because the recombinant peptabody of Houimel *et al.* differs from that of the instant invention in terms of both sequence and structure.

With regard to sequence identity, Applicants note that neither the COMP sequence nor the hinge sequence of the instant invention are identical to those presented in Houimel *et al.* as particularly alleged by the Examiner. For example, page 749, column 2, lines 14-15 of Houimel *et al.* teaches that the N-terminal end of their COMP amino acid sequence begins with the sequence SGDLGP (differing amino acid underlined). In contrast, the instant amended claim 1, which is representative of instant amended independent claims 43, 44, 49, and 59, recites "a cartilage oligomer matrix polypeptide consisting of amino acid residues 16 to 64 of SEQ ID

NO:2…" Applicants respectfully direct the Examiner's attention to SEQ ID NO:2, which discloses a COMP sequence wherein the N-terminal amino acid sequence differs from that of Houimel *et al.* Therefore, in contrast to the Examiner's allegation, the composition of the COMP sequence present in the peptabody of Houimel *et al.* is not identical to the composition of the COMP protein of the instant claims. Furthermore, Applicants note that the hinge region of the peptabody disclosed by Houimel *et al.* is not identical to the sequence claimed in the instant invention. For example, Houimel *et al.* recites a hinge of sequence PSTPPTPSPSTPPTPSP (page 749, column 2, line 13). In contrast, instant amended claim 1 recites, in part, "a hinge region of an immunoglobulin polypeptide having the amino acid residues 65 to 83 of SEQ ID NO:2." Applicants respectfully direct the Examiner's attention to sequence set forth as SEQ ID NO:2, which discloses that the hinge region of the instant invention has the following amino acid sequence: TSPPTPPTPSPSTPPTPSP (differing residues are underlined). Therefore, in contrast to the Examiner's allegation, the hinge sequence taught by Houimel *et al.* is not identical to the hinge sequence claimed in the instant invention. The Examiner will also note that Applicants have amended claim 1, which is representative of instant amended independent claims 43, 44, 49, and 59, to delete the 'comprising' language that referred to the COMP and hinge sequences to further clarify the subject matter being claimed. In view of this, Applicants respectfully submit that Houimel *et al.* does not teach or suggest either the COMP polypeptide or hinge elements of the instant inventions, as presently claimed.

With regard to the overall structure of the molecule described in the cited art structure, Applicants note that Houimel *et al.* teaches a peptabody of the following structure: anti-ErbB-2 hexapeptide/hinge/COMP/hinge/6X His tag (see Figure 2A). Applicants respectfully submit that instant amended claim 1, which is representative of instant amended independent claims 43, 44, 49, and 59, teaches a peptabody with the general structure enhancer/COMP/hinge/EGFR ligand, which is not identical to that taught by Houimel *et al.* It is Applicants' position that this structure imparts functional characteristics to the peptabody that are neither taught nor suggested by the peptabody of Houimel *et al.* For example, the claimed peptabody targets ErbB-1, ErbB-3, and ErbB-4, whereas the peptabody of Houimel *et al.* does not. Additionally, the claimed peptabody utilizes natural EGFR ligands rather than the short synthetic hexapeptide ligands present in the peptabody of Houimel *et al.* Without being bound by any particular theory, Applicants believe that the use of these natural ligands increases the affinity of the

peptabody/target interaction, relative to similar interactions with shorter synthetic peptides. Additionally, the peptabody of the instant invention results in efficient induction of apoptosis. In contrast, the peptabody of Houimel *et al.* was not shown to be able to induce apoptosis, rather, it was only shown to inhibit cellular proliferation (see *e.g.* Figure 7). In view of this, Applicants respectfully submit that not only does Houimel *et al.* fail to teach or suggest either the COMP polypeptide or hinge elements of the instant invention, it fails to teach a recombinant peptabody of a similar structure and function to that presently claimed. Given this, Applicants respectfully submit that the recombinant peptabody of Houimel *et al.* should not serve as the basis for a rejection under 35 U.S.C. § 103(a) because: it fails to teach each and every element of the instant invention as presently claimed; it fails to teach a recombinant peptabody of the presently claimed structure; and it fails to teach a recombinant peptabody with the presently claimed function.

Even if Houimel *et al.* did disclose a recombinant peptabody with the same COMP and hinge region sequences, same structure, and same function as that claimed, which it does not, the Examiner has admitted that the reference does not teach the enhancer sequences of SEQ ID NO's 5, 6, and 9. To counter this deficiency, the Examiner has offered Wickham *et al.*, which recites a peptide ligand of the sequence YSFEDLYRR. It is the Applicants' position that the Examiner's use of Wickham *et al.* is inappropriate to establish a *prima facie* case of obviousness because the art disclosed by the reference is completely non-analogous to the instant invention. Wickham *et al.* discloses the use of a YSFEDLYRR peptide as non-native ligand that can be expressed as part of an adenoviral coat protein in order to facilitate selective targeting of a recombinant adenovirus (page 2, paragraph 15). In contrast, the instant application teaches that the YSFEDLYRR peptide mediates efficient production of the peptabody in *E. coli*, and does not address any functional role of the peptide sequence in either cell binding or cell internalization, which is the central purpose of the peptide disclosed in Wickham *et al.* Applicants are hard pressed to see how one of ordinary skill in the art could read Wickham *et al.* and come to the conclusion that it would be a good idea to incorporate the YSFEDLYRR peptide disclosed therein into a recombinant peptabody construct for the purpose of facilitating the bacterial expression of such a peptabody construct: there is simply no disclosure in Wickham *et al.* that would teach, suggest, or motivate one of ordinary skill in the art to arrive at that conclusion. Applicants respectfully submit that the Examiner's identification of the Wickham *et al.* reference could only have been made in hindsight, with the benefit of the instant invention.

As such hindsight reconstruction is not allowed, Applicants respectfully request that the Wickham *et al.* reference be removed from consideration.

For the foregoing reasons, Applicants respectfully submit that Houimel *et al.* does not teach or suggest a recombinant fusion peptabody as particularly claimed in the instant amended claims 1, 43, 44, 49 and 59. Furthermore, Applicants have also amended these five independent claims to indicate that the epidermal growth factor receptor ligand is "selected from the group consisting of any of SEQ ID NOs:10-29 and amino acid residues 86 to 138 of SEQ ID NO:2" which further differentiates the instant invention from the disclosure of Houimel *et al.*, or any of the other cited references. In view of these amendments, Applicants submit that the claimed recombinant peptabodies include specific elements defined by specifically defined polypeptide sequences. Consequently, the peptabodies of the instant invention as particularly claimed have both different compositions and structures than the peptabody of Houimel *et al.* Applicants further submit that these differences in composition and structure result in an improved peptabody with novel functional characteristics that are neither taught nor suggested by Houimel *et al.*

In view of the above described deficiencies in Houimel *et al.* and Wickham *et al.*, Applicants respectfully submit that none of the cited references either alone or in combination, teach or suggest all of the elements of the peptabody as particularly claimed in instant amended claims 1, 43, 44, 49, and 59; consequently, the Examiner has failed to establish a *prima facie* case of obviousness. Applicants respectfully request that this rejection be withdrawn.

The Examiner has further rejected claims 1, 4, 8-10, 12, 17, 28-30, 43-46, 49, 50, 53-60, and 63-68 under 35 U.S.C. § 103(a) as being unpatentable over Houimel *et al.* 2001 in view of Wickham *et al.* 2002, Koh 2006, Rush *et al.* 1996, and Todaro *et al.* 1986, in further view of Rosen *et al.* 2001 (U.S. Patent No. 6,926,898). Applicants respectfully submit that the above described deficiencies in Houimel *et al.* and Wickham *et al.* are not overcome by the teachings of Rosen *et al.*, which teaches an albumin protein fused to anti-ErbB-2 antibodies, and does not teach or suggest the recombinant peptabody of the instant invention. In view of the foregoing arguments, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested. If there are any remaining issues, or if the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

The Commissioner is hereby authorized to charge any deficiency in the fees paid herewith, or credit any overpayment, to Deposit Account No. 12-0080 under Order No. KZY-002USRCE, from which the undersigned is authorized to withdraw.

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Respectfully submitted,

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